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Brief report

Vinorelbine in pre-treated advanced head & neck squamous cell carcinoma

A phase II study

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Key words: head & neck cancer, phase II study, vinorelbine

Summary

Background: There are few moderately active single-agents for the treatment of recurrent or metastatic head & neck cancer. Thus, the identification of novel active agents is warranted. We performed the present phase II trial to evaluate activity and toxicity of vinorelbine (VNB) in previously treated patients with advanced head & neck cancer. *Patients and methods*: 16 patients entered the study, 15 of whom were evaluable. The main characteristics were: M/F = 14/1; median age of 58 yrs (18–67); median PS (Karnofsky score) of 70 (60–100); primitive tumor sites were: oropharynx in 5; larynx in 4, hypopharynx in 3, rhynopharynx in 2, and oral cavity in 1 patient; initial clinical stage was IV in 9, III in 4 and II in 2 patients. Previous treatments were: cisplatinum with concurrent radiotherapy in 6 and cisplatinum + fluorouracil (for at least 2 cycles) in 9 patients. VNB was given at the dose of 20 mg/m^2 i.v. infusion for 1 hr, weekly, for a minimum of 8 doses. Response and toxicity were evaluated after at least 8 doses of VNB. *Results*: Overall, 139 courses of VNB were given (median 9, range 8–19). Objective responses were: partial response in 1 patient (6%); stable disease, lasting at least 2 months, in 4 patients (27%) and progression in the other 10 patients (67%). Three patients had a one week delay in subsequent courses due to severe hematological toxicity. Toxicities observed were: leucopenia of grade IV (W.H.O.) in 2 patients and of grade I–II in 12 patients; granulocytopenia of grade III in 1 patient and of grade IV in 2 patients; grade I–II anemia in 4 patients; grade II phlebitis in 3 patients; grade II constipation in 2 patients, grade I–II peripheral neuropathy in 3 patients, grade I–II nausea and vomiting in 4 patients, and grade II stomatitis in 2 patients. *Conclusions*: VNB, in this series of heavily pre-treated patients with head & neck cancer, did not reveal an antitumor activity of interest.

Introduction

Recurrent and/or metastatic head and neck squamous cell carcinoma is not curable and chemotherapy only has a palliative role. Single-agents with moderate activity (ranging from 20 to 41%) are cisplatinum, carboplatin, methotrexate and bleomycin (see ref. 1 for a review). However, none of these agents is able to improve survival. Consequently, patients with recurrent and/or metastatic head & neck cancer are candidates for phase I–II trials of new antiproliferative agents [1]. Vinorelbine (VNB) (Navelbine, Pierre Fabre Medicament, Boulogne, France) is a semisynthetic vinca alkaloid which differs from vinblastine by a modification of the catharantine moiety of the molecule [2]. It possesses a selective affinity for myototic tubuline-associated protein. In experimental *in vivo* studies VNB was found to be active against two squamous cell lung carcinomas (QG56 and LC06) as well as against other solid tumors [3]. Data from phase I trials have shown that using a weekly schedule of administration, the maximum tolerated dose of VNB, in patients pre-treated with

chemotherapy, ranged from 20 to 35 mg/m^2 [4]. Subsequently, phase II trials demonstrated that VNB is a new active agent for breast cancer [5] and non-small-cell lung cancer [6]. We conducted this disease-oriented phase II trial in order to determine the activity of this novel drug in patients with pre-treated squamous cell carcinoma of the head & neck.

Patients and methods

Patient selection

All patients entered into this study had histological diagnosis of squamous cell carcinoma of the head & neck, they were pre-treated with chemotherapy ± radiotherapy and had progressive disease. All gave informed consent for the therapy. Additional eligibility criteria were: measurable disease, Karnofsky performance status ≥ 60, a life expectancy greater than 8 weeks, adequate hematologic (WBC count > 4,000/mm^3, platelet count > 120,000/mm^3) renal (creatinine < 1.5 mg% and bun < 30 mg%) and hepatic (bilirubin < 1.5% and alkaline phosphatase and/or SGOT and SGPT ≤ 2 × upper limits of normal) functions.

Preireatment evaluation of patients included: complete history and physical examination, with measurement of all neoplastic lesions, chest x-ray, complete blood count and serum biochemical profile. A blood count was required prior to each administration of the drug. Parameter lesions were re-evaluated by physical examination and radiological studies after two months of treatment and then were systematically repeated every 2 months or whenever indicated by individual clinical situations.

Treatment plan

NVB was supplied in 10 mg vials by Pierre Fabre Medicament. The drug was diluted in 500 mg of saline solution and administered by intravenous (i.v.) infusion of 60 min, every week, until progression or toxicity for at least 8 courses. A cycle was defined as 4 courses or weeks of treatment. The given dose was of 20 mg/m^2 every 7 days. The courses were postponed by 1 week if grade III–IV hematological toxicity occurred, without dose reduction.

Table 1. Patients characteristics

No. of entered patients	16
No. of evaluable patients	15
Male/female	14/1
Median age (range), yrs	58 (18–67)
Median performance status*	70 (60–100)
Site of primary	
Oropharynx	5
Larynx	4
Hypopharynx	3
Rhynopharynx	2
Oral cavity	1
Sites of measurable disease	
Primary	5
Locoregional lymph nodes	2
Primary + lymph nodes	4
Distant metastasis	4
Previous treatments	
Concomitant cisplatinum-radiation therapy	6
Cisplatinum-fluorouracil + surgery ± radiation therapy	9

*Karnofsky score.

Study parameters

The primary objective of this phase II-oriented study was to determine the activity and acute and subacute toxicity of VNB. The World Health Organization (W.H.O.) criteria for response and toxicity evaluation were employed [7]. An assessment of tumor size was made in patients with measurable disease by measuring the sum of the two maximum diameters of each lesion, prior and after at least 8 doses (2 cycles) of treatment with VNB, to define tumor objective responses according to standard W.H.O. criteria [7]. Briefly: complete remission (CR), complete disappearance of all measurable lesions, for at least 4 weeks; partial remission (PR), ≥ 50% reduction in measurable diameter of all lesions; progressive disease (PD), ≥ 25% increase in measurable lesions and/or appearance of any new lesion and; stable disease (SD), < 50% reduction in measurable diameter of all lesions or < 25% increase in measurable lesion, lasting at least 8 weeks.

Statistical analysis

The Gehan two step procedure [8] was used to determine *a priori* the number of patients to be included in the study, using a rejection error of 5% and a standard error of 10% in assessing response rate to the treatment.

Results

Sixteen consecutive patients, observed at our Center from September 1992 to September 1993, entered the study. Patient characteristics and previous therapies are listed in Table 1. Fifteen patients were fully evaluable for response and toxicity, after treatment with VNB. One patient was not evaluable because of treatment refusal due to psychological discomfort after the first 4 doses of VNB. He also refused subsequent proposed treatments and died from progressive disease 3 months later.

Sites of measurable lesions were: locoregional in 11 cases (neck lymph nodes in 2, recurrent primary in 5 and both in 4) and distant metastasis in 4 cases (3 lung and one soft tissue diffusion).

As far as previous treatments are concerned, 6 patients with unoperable locally advanced disease (stages III–IV) received concurrent cisplatinum and radiation therapy. With such a combined therapy 2 patients obtained a CR, three a PR and one had PD. Nine patients received surgery ± radiation therapy followed by at least two courses of cisplatinum and fluorouracil. With such a chemotherapeutic regimen one patient achieved a CR, 2 a PR, whereas 6 had PD. Of these, two patients received a second line chemotherapy with methotrexate and bleomycin. The median interval period between the end of prior therapy and protocol entry was of 8 months (range, 2 to 17).

A total of 139 courses of NVB were administered for a median of 9 cycles per patient (range 8–19).

Objective responses obtained with VNB were: 1 PR, lasting 10 weeks, in a patient with UICC-TNM T3N3Mo (stage IV) carcinoma of the oropharynx previously treated with surgery, radiation therapy and 3 courses of cisplatinum-fluorouracil; recurrent evaluable sites for response were neck lymph-nodes; a SD, lasting at least 8 weeks was observed in 4 patients (the duration of response was of 10, 12, 17 and 21 weeks, respectively), the other 10 patients had PD; three patients had at least a one week treatment delay due to the occurrence of grade III–IV hematological toxicity; the median time to progression was of 8 weeks (range, 8 to 22+) and the median survival of the series was of 18 weeks (range, 8 to 70+).

Leukopenia was the most important and frequent toxic effect of VNB. Overall, 14 cases had hematological toxicity. Two patients had grade IV leukopenia and granulocytopenia (nadir of WBC: 900/mm^3 and 600/mm^3, respectively, and nadir of granulocytes: 300/mm^3 and 400/mm^3, respectively). Both the patients were promptly hospitalized, treated with G-CSF s.c. and one also required antibiotic therapy for fever and pneumonia. In these two patients a complete hematological recovery was obtained after 7 and 10 days, respectively. The other 12 patients had transient grade I–II leukopenia and 1 patient had grade III granulocytopenia (nadir: 900/mm^3). The median leukocyte and granulocyte count nadirs were 3,300 (range, 600 to 6,700) and 1,200 (range, 300 to 4,600), respectively. Four cases developed moderate (grade I–II) anemia. No patient developed thrombocytopenia. Non-hematologic toxicity was moderate. Three patients had grade II chemical phlebitis, 2 patients had grade II constipation and 3 patients had grade I–II transient peripheral neuropathy. Grade I–II nausea and vomiting was seen only in 4 patients. Finally, only two cases had grade II stomatitis.

Discussion

In accordance to the Gehan [8] two-step procedure, using a rejection error of 5% and a standard error of 10%, this study demonstrates that the response rate to VNB, in our series of pre-treated patients with head & neck cancer, is less than 20% (1 major objective response out of 15 evaluable patients). Therefore the present study should be considered as a negative phase II trial. The observation that the majority of the patients treated with VNB developed hematologic toxicity, with two cases who experienced grade IV leukopenia and granulocytopenia and one additional patient who had grade III granulocytopenia, indicates that an

adequate dose of the drug was given in this series of heavily pre-treated patients. At our knowledge there is only one other published phase II study reporting on VNB in this neoplasia. In the series of Gebbia *et al.* [9] VNB had a moderate activity. In fact, 5 out of 23 patients (22%) achieved a partial response. The different results obtained in the two studies may be explained by the evidence that they differ for several reasons. Mainly: 1) the selection criteria of the patients were different. While all our cases were pre-treated and had received at least one previous chemotherapy, the large majority of the cases (75%) of the Gebbia *et al.* series [9] were treated with surgery or radiation therapy alone; 2) the characteristics of the patients were different concerning the site of the primary, initial stage and site of the evaluable recurrent disease. In particular, in Gebbia's study [9] among the responders there were two patients with loco-regional disease from oropharynx, two from laryngeal cancer and one presenting tissue metastasis of the rhinopharynx. It is known that responsiveness of head and neck cancers to radiotherapy and chemotherapy may differ depending on the site and histology of the primary [10]. Finally; 3) the majority of the patients (20 of 24) treated in the study of Gebbia *et al.* [9] received a dose of 25 mg/m^2. However, the authors did not make mention if treatment delays were necessary due to toxic side-effects, so the dose intensity of our study is not comparable with that of Gebbia's trial. However, a common finding was that Gebbia *et al.* [9] did not report major objective responses in any of the patients pre-treated with chemotherapy.

We conclude that VNB, in heavily pre-treated advanced head & neck squamous cell carcinoma, at the dose and schedule administered in this study, did not reveal a useful antitumor activity.

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